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OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

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From: David Nadrchal, Chemist *David Nadrchal*
Risk Assessment Branch (RAB) V
Health Effects Division (HED; 7509P)

Through: Michael Metzger, Branch Chief *Michael L. Metzger*
Risk Assessment Branch V/VII
Health Effects Division (HED; 7509P)

To: Danette Drew, Chemist, Risk Assessor
Risk Assessment Branch V
Health Effects Division (HED, 7509P)

Julie Javier, Chemical Review Manager
Dana Friedman, Acting Branch Chief
Risk Management and Implementation Branch 1
Pesticide Re-Evaluation Division (7508P)

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1.0 Executive Summary

MCPA (4-chloro-o-tolxyloxyacetic acid) is an herbicide having established U.S. tolerances on a variety of crops and grasses. This phenoxy herbicide acts by simulating the action of natural hormones to produce uncoordinated cell division and plant growth in susceptible weeds. End-use products of MCPA are formulated in either salt, ester, or amine forms. MCPA is often used in mixture with many other products to achieve a wider spectrum of weed control. The qualitative nature of the residue in primary crops as well as livestock and rotation crops is adequately understood. The residues of concern for risk assessment in plants are MCPA and its metabolite 2-HMCPA (4-chloro-2-hydroxymethylphenoxyacetic acid) while livestock and drinking water are MCPA only. Tolerances are established in 40 CFR §180.339 (a) 1) and 2) for residues of MCPA only. Current MCPA tolerances range from 0.1 ppm to 300 ppm. Adequate enforcement methods are available for the determination of residues in/on plant and animal commodities.

The MCPA Task Force Three has submitted a recent cattle feeding study which updated feed to tissue transfer ratio with information that reflected estimated dietary burdens (MRID No. 47075201). A reassessment of the dietary burden was subsequently performed to consider residues in all feed commodities using the Dietary Burden Calculator PMRA v.2.8, which is based on the Guidance Document on Residues in Livestock, 04-SEP-2013 (OECD ENV/JM/MONO(2013)8). The re-estimated expected residues in livestock commodities were higher, lower, or similar to those used to establish the tolerances in milk and meat. Therefore, the current recommended tolerances reflect these updates.

Tolerance expression has been updated to comply with *Guidance on Tolerance Expressions* (S. Knizer, 5/27/2009) and place all tolerances under 40 CFR§180.339 (a). Several tolerances were increased or decreased based on updated OECD calculations, to harmonize with Codex, or to reflect HED Rounding Class Practice. HED is recommending tolerances which range from 0.01 ppm to 500 ppm. The scoping document of MCPA included a summary of data deficiencies of the residue chemistry (A. LaMay, D414988, February 6, 2014). These residue chemistry data deficiencies resolved.

2.0 Regulatory Recommendations

HED recommends that the uses for direct application to alfalfa and clover be removed from the MCPA labels or crop field trial residue data should be submitted to support those uses due to data deficiencies outlined in section 2.1. Current tolerances listed for alfalfa and clover are appropriate to small grains underseed uses.

2.1 Data Deficiencies/Data Needs

There are adequate residue data to support the application of MCPA to small grains underseeded with alfalfa or clover (D. Drew, D4273232, May 27, 2015). There are no residue data to support the direct application of MCPA to alfalfa and clover stands which could result in higher residues than applications to an underseeded crop. The alfalfa and clover crop field trials should be

performed according to the 860.1500 Guideline.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

For enforcement of tolerances for residues of MCPA, PAM Vol. II lists PAM Vol. I Sections 221.1, 421, and 422. No limit of quantitation is specified. We note that Section 221.1 has now become Section 402 (GC method for acids and phenols) and Sections 421 and 422 (TLC methods) no longer exist. The Residue Chemistry Chapter of the Registration Standard dated 8/31/81 noted that the PAM Vol. I method is adequate for enforcement of tolerances for residues of MCPA in livestock commodities as-is but recommended that the method be modified with a hydrolysis step for enforcement of MCPA tolerances for plant commodities. The current PAM Vol II methods are adequate for the enforcement of MCPA on plants and livestock commodities and no further modifications are required at this time. The data requirement for 860.1340 residue analytical methods is fulfilled.

2.2.2 Recommended Tolerances

Tolerances for residues of MCPA are currently expressed in terms of MCPA per se (40 CFR §180.339). MCPA residues of concern in plant and animal commodities had been previously determined to include MCPA and its metabolite, 2-HMCPA for risk assessment and MCPA only for tolerance enforcement (MARC, D308991, October 7, 2004). The tolerance definition for MCPA residues should be updated to comply with *Guidance on Tolerance Expressions* (S. Knizer, 5/27/2009) to read as follows:

“(a) General. Tolerances are established for residues of the herbicide MCPA, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only MCPA, 2-(4-chloro-2-methylphenoxy)acetic acid, in or on the commodity.”

This tolerance definition should cover all recommended tolerances under 40 CFR §180.339 (a)(1) as the tolerance expression is the same for plant and livestock commodities. A summary of the MCPA tolerance reassessment for the animal and crop commodities and recommended modifications in commodity definitions are presented in Table 2.2.2.

Table 2.2.2. Tolerance Summary for MCPA.			
Commodity	Established/ Proposed Tolerance (ppm)	HED- Recommended Tolerance (ppm)	Comments
Alfalfa, forage	0.5	0.50	Corrected value to be consistent with HED Rounding Class Practice.
Alfalfa, hay	2.0	2.0	
Barley, grain	1.0	0.20	Updated OECD calculation. Harmonization with Codex

Barley, hay	40	50	Harmonization with Codex
Barley, straw	25	50	Harmonization with Codex
Cattle, fat	0.1	0.20	Updated dietary burden. Corrected value to be consistent with HED Rounding Class Practice. Harmonization with Codex
Cattle, meat	0.1	0.10	
Cattle, meat byproducts	0.1	3.0	
Clover, forage	0.5	0.50	Corrected value to be consistent with HED Rounding Class Practice.
Clover, hay	2.0	2.0	
Flax, seed	0.1	0.01	Updated residue data. Harmonization with Codex
Goat, fat	0.1	0.20	Updated dietary burden. Corrected value to be consistent with HED Rounding Class Practice. Harmonization with Codex
Goat, meat	0.1	0.10	
Goat, meat byproducts	0.1	3.0	
Grain, aspirated fractions	3.0	3.0	
Grass, forage, fodder, and hay, Group 17, forage	-	500	Updated OECD calculation. Updated to Group Tolerance. Harmonization with Codex
Grass, forage	300	Remove	
Grass, forage, fodder, and hay, Group 17, hay	-	200	Updated OECD calculation. Updated to Group Tolerance
Grass, hay	20	Remove	
Hog, fat	0.1	Remove	Updated dietary burden. No expectation of quantifiable residues
Hog, meat	0.1	Remove	
Hog, meat byproducts	0.1	Remove	
Horse, fat	0.1	0.20	Updated dietary burden. Corrected value to be consistent with HED Rounding Class Practice. Harmonization with Codex
Horse, meat	0.1	0.10	
Horse, meat byproducts	0.1	3.0	
Lespedeza forage	0.5	0.50	Corrected value to be consistent with HED Rounding Class Practice.
Lespedeza, hay	2.0	2.0	
Milk	0.1	0.04	Updated dietary burden. Harmonization with Codex
Oat, forage	20	50	Harmonization with Codex
Oat, grain	1.0	0.20	Updated OECD calculation. Harmonization with Codex
Oat, hay	115	50	Updated OECD calculation. Harmonization with Codex
Oat, straw	25	50	Harmonization with Codex
Pea, dry, seed	-	0.01	Commodity definition revision. Updated field trial data.
Pea, dry	0.1	remove	
Pea, field, hay	0.1	1.5	Updated field trail data

Pea, succulent shelled	-	0.10	Commodity definition revision. Corrected value to be consistent with HED Rounding Class Practice.
Pea, succulent	0.1	remove	
Pea, field, vines	0.1	0.60	Updated field trial data
Rye, forage	20	50	Harmonization with Codex
Rye, grain	1.0	0.20	Updated OECD calculation. Harmonization with Codex
Rye, straw	25	50	Harmonization with Codex
Sheep, fat	0.1	0.20	Updated dietary burden. Corrected value to be consistent with HED Rounding Class Practice. Harmonization with Codex
Sheep, meat	0.1	0.10	
Sheep, meat byproducts	0.1	3.0	
Trefoil, forage	0.5	0.50	Corrected value to be consistent with HED Rounding Class Practice.
Trefoil, hay	2.0	2.0	
Vetch, forage	0.5	0.50	Corrected value to be consistent with HED Rounding Class Practice.
Vetch, hay	2.0	2.0	
Wheat, forage	20	50	Harmonization with Codex
Wheat, grain	1.0	0.20	Updated OECD calculation. Harmonization with Codex
Wheat, hay	115	50	Updated OECD calculation. Harmonization with Codex
Wheat, straw	25	50	Harmonization with Codex

2.2.3 Revisions to Tolerances

D. Drew, D437360, June 14, 2017

D45288704.der

D46242401.der

The MCPA Task Force Three submitted a crop field trial study reflecting the use of MCPA on dry peas (MRID 50107601; Guideline 860.1500) in response to outstanding residue chemistry data requirements. HED has evaluated the dry pea data submitted, along with existing field trial data on succulent peas, and concluded that there was sufficient data with adequate geographical representation to support a national use of MCPA on peas, and to support the current tolerance of 0.10 ppm for succulent peas. Dry pea residues from field trials were <0.010 ppm following applications approximating the 1x rate. These data indicate that the current tolerance of 0.1 ppm for pea, dry is too high and a tolerance at the method LOQ of 0.01 ppm is recommended and is harmonized with Codex Maximum Residue Limit (MRL). The recent data also indicated that the current tolerance of 0.1 ppm for MCPA on pea hay and vines was too low. A tolerance level of 0.60 ppm for pea vines and 1.5 ppm for pea hay was recommended.

HED has reviewed tolerances for grass, forage and grass, hay and has determined that current tolerances were too low. Upon review of the crop field trial study reflecting the use of MCPA on pasture and rangeland, grass showed residues of MCPA at preharvest intervals (PHIs) of 0, 7, 14, 21, and 30 days (MRID 45288704; Guideline 860.1500). In addition, the required variety of grasses were tested (bermuda, fescue, and brome) to establish a group tolerance. Using the OECD calculation procedure for these results in a tolerance level of 200 ppm for grass, forage

and 400 ppm for grass, hay (Appendix C. OECD MRL Calculation Procedure Inputs/Outputs). Recommended tolerance for grass, hay is 500 ppm to harmonize with Codex MRLs.

HED has reviewed tolerances for flax, wheat, grain and wheat, hay and has determined that current tolerances were too high. Upon review, crop field trial studies reflecting the use of MCPA on wheat showed residue levels that were lower than current tolerances (MRID 45763101; Guideline 860.1500). The study used exaggerated rates (2x label rate) of MCPA DMAS, MCPA 2-EHE, and MCPA NA on wheat crops in the United States. Using the OECD calculation procedure for these results in a recommended tolerance level of 0.20 ppm for wheat, grain and 40 ppm for wheat, hay (Appendix C). Wheat, hay tolerance recommendation was 50 ppm to harmonize with Codex MRLs. These values were translated to barley, oat, and rye crops based on previous translation decisions.

Flax crop field trial data (MRID 46242401; Guideline 860.1500) had been received and were reviewed by HED. The recent data indicated that the current tolerance of 0.1 ppm was too high. All samples collected were below the method limit of quantification (LOQ) of 0.025 ppm. To harmonize with Codex, a tolerance of 0.01 ppm is recommended as more recent field trial data were available from Canada with a lower LOQ of 0.01 ppm and a higher application rate (2x U.S. field trial data). These data were reviewed in the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) report number 257 for MCPA reviewed in 2012.

Hog and ruminant products and milk tolerances were updated due to new data received from the MCPA Task Force Three (MRID 47075201; Guideline 860.1480) and updates using the latest dietary burden calculations. See section 5.2.2.2 Estimated Secondary Residues in Livestock for more detailed information.

2.2.4 International Harmonization

Canada, Codex, and the U.S. have the same MCPA residue definition; residues of both free and conjugated are regulated (See Appendix B). There are currently no established MRLs from Codex or Canada for alfalfa, clover, lespedeza, trefoil, or vetch commodities. No tolerances are proposed for poultry, eggs, or hogs due to the reasonable expectation of no quantifiable residues in those commodities (see section 5.2.2.2 Estimated Secondary Residues in Livestock). Ruminant products and milk tolerances were updated and harmonized with Codex levels. Grass forage and hay tolerances were updated using the OECD calculation procedure and hay was harmonized with the Codex MRL. Tolerances for the forage, grain, hay, and straw of barley, oat, rye, and wheat were also harmonized with Codex levels. Flax seed was harmonized to the lower level of 0.01 ppm due to more recent field trial data from Canada with a similar use pattern and lower LOQs. Pea, dry was harmonized with Codex to the lower level of 0.01 ppm due to recent field trial data showing residues of MCPA below the method LOQ (0.010 ppm).

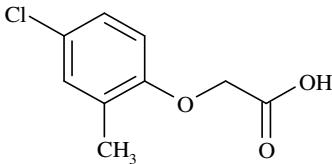
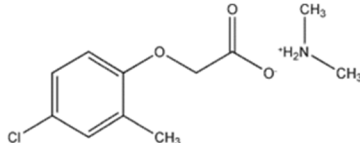
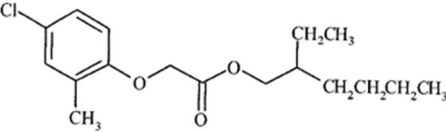
2.3 Label Recommendations

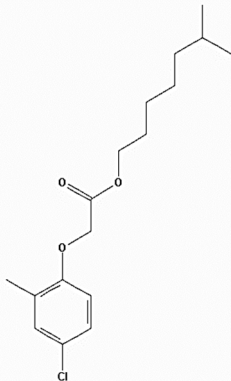
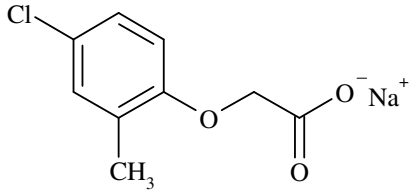
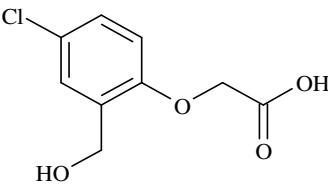
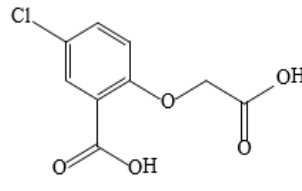
HED recommends that the uses for direct application to alfalfa and clover be removed from the MCPA labels.

3.0 Introduction

MCPA (2-methyl-4-chlorophenoxyacetic acid) is a selective, post-emergence systemic herbicide used for the control of annual and perennial broadleaf weeds. MCPA is a phenoxy herbicide registered for use on alfalfa, barley, clover, flax, oats, pasture and rangeland grass, peas, rye, triticale, and wheat, as well as grass grown for seed, to control a variety of broadleaf weeds. MCPA is also registered for use on turf, lawns, golf courses, and rights-of-way. This phenoxy herbicide acts by simulating the action of natural hormones to produce uncoordinated cell division and plant growth in susceptible weeds. End-use products of MCPA are formulated in either salt, ester, or amine forms.

3.1 Chemical Identity

Table 3.1. MCPA Nomenclature and Metabolite of Interest.	
Compound	Chemical Structure 
Common name	MCPA
IUPAC name	4-chloro-o-tolyloxyacetic acid
CAS name	2-(4-chloro-2-methylphenoxy)acetic acid
CAS #	94-74-6
PC Code	030501
Compound	Chemical Structure 
Common name	MCPA dimethylamine salt (DMA)
IUPAC name	(4-chloro-2-methylphenoxy)acetic acid, dimethylamine salt
CAS name	(4-chloro-2-methylphenoxy)acetic acid, compound with N-methylmethanamine (1:1)
CAS #	2039-46-5
PC Code	030516
Compound	Chemical Structure 
Common name	MCPA 2-ethylhexyl ester (2-EHE)
IUPAC name	2-ethylhexyl 2-(4-chloro-2-methylphenoxy)acetate
CAS name	(4-chloro-2-methylphenoxy)acetic acid, 2-ethylhexyl ester
CAS #	29450-45-1
PC Code	030564

Compound	
Common name	MCPA, isooctyl ester
IUPAC name	6-methylheptyl 2-(4-chloro-2-methylphenoxy)acetate
CAS name	2-(4-chloro-2-methyl-phenoxy)acetic acid 6-methylheptyl ester
CAS #	26544-20-7
PC Code	030563
Compound	Chemical Structure 
Common name	MCPA sodium salt (Na)
IUPAC name	sodium 4-chloro-o-tolyloxyacetate
CAS name	sodium 2-(4-chloro-2-methylphenoxy)acetate
CAS #	3653-48-3
PC Code	030502
Metabolite	Chemical Structure 
Common name	2-HMCPA
IUPAC name	4-chloro-2-hydroxymethylphenoxyacetic acid
Metabolite	Chemical Structure 
Common name	CCPA
IUPAC name	2-carboxy-(4-chlorophenoxy)acetic acid
CAS name	2-carboxy-4-chlorophenoxyacetic acid

3.2 Physical/Chemical Characteristics

MCPA acid is a white to light brown solid, flake, or microcrystalline powder with a melting point of 114-119 °C, density of 1.18-1.21 g/ml at 20°C, octanol/water partition coefficient (log K_{ow}) of 2.73, and vapor pressure of 7.7×10^{-6} mbar at 20°C. MCPA is practically insoluble in water (0.03 g/100 g at 20°C) and is soluble in a range of organic solvents including acetone (91.8 g/100 g), ethyl ether (50.2 g/100 g), chloroform (5.5 g/100 g), and benzene (3.3 g/100 g).

MCPA DMA is a pale yellow or yellowish-white liquid with a boiling point of 111°C, density of 1.181 at 20°C, and octanol/water partition coefficient (log K_{ow}) of 1.415 at 25°C. MCPA DMA rapidly dissociates in an aqueous medium to form the free phenoxy anion moiety and the dimethyl ammonium ion.

MCPA 2-EHE is an amber to brown liquid with a boiling point of 260-265°C, bulk density of 8.9 lb/gal (1.06 g/mL specific gravity), octanol/water partition coefficient (K_{ow}) of 5.37, and vapor pressure of 1.77×10^{-5} mbar at 20°C. MCPA 2-EHE is practically insoluble in water (<1 mg/L) and is miscible with most organic solvents and in mineral oils.

No chemical identification information is available concerning the MCPA Na salt, except that it is water soluble.

Table 3.2. Physicochemical Properties of MCPA.

Parameter	Value			Reference
	MCPA	MCPA DMAS	MCPA 2-EHE	
Melting point/range (Boiling point/range)	114-119 °C	(111 °C)	(260-265 °C)	MCPA RED, PC Chapter
pH	approximately 3 [MCPA Reregistration Standard, PC Chapter]	Not available	3.46 at 19.7 °C [D202560]	[See specific column]
Density, at 20 °C	1.18-1.21 g/mL	1.181 g/mL	8.9 lb/gal bulk density (1.06 g/mL specific gravity)	MCPA RED, PC Chapter
Water solubility, at 20 °C	0.03 g/100 g	Rapidly dissociates to the free phenoxy anion and dimethyl ammonium ion in water.	<1 mg/L	MCPA RED, PC Chapter
Solvent solubility, at 20 °C	91.8 g/100 g acetone 50.2 g/100 g ethyl ether 5.5 g/100 g chloroform 3.3 g/100 g benzene	Not available	Miscible in most organic solvents and mineral oils.	MCPA RED, PC Chapter

Table 3.2. Physicochemical Properties of MCPA.				
Parameter	Value			Reference
	MCPA	MCPA DMAS	MCPA 2-EHE	
Vapor pressure, at 20 °C	7.7×10^{-6} mbar	Not available	1.77×10^{-5} mbar	MCPA RED, PC Chapter
Dissociation constant, pK_a	3.07	Not available	Not available	CB# 923, 9/12/86, W. Anthony [Task Force Data; Accession No. 962678]
Octanol/water partition coefficient, $\text{Log}(K_{ow})$	2.73	1.415	5.37	MCPA RED, PC Chapter
UV/visible absorption spectrum	Not available	Not available	Absorbance peaks observed at 203, 228, and 279 nm for a solution of MCPA 2-EHE in water with methanol co-solvent; molar absorption coefficient of $16784 \text{ M}^{-1} \text{ cm}^{-1}$ at λ_{MAX} 203.1 nm.	D202560

3.3 Pesticide Use Pattern/Directions for Use (860.1200)

The registered uses of MCPA are summarized in the Line by Line, and Maximum Use Scenario Pesticide Label Usage Summary (PLUS) Reports as generated by OPP's Biological and Economic Analysis Division (BEAD).

Conclusions.

HED recommends that the uses for direct application to alfalfa and clover be removed from the MCPA labels. There are no residue data to support the direct application of MCPA to alfalfa and clover stands which could result in higher residues than applications to an underseeded crop which have supporting data.

4.0 Metabolite/Degradate Residue Profile

4.1 Nature of the Residue

4.1.1 Summary of Plant Metabolism (860.1300)

D. Nadrchal, D442968, January 25, 2018.

Data deficiencies were previously identified for the metabolism of MCPA on peas. The MCPA Task Force Three proposed previously submitted data of MCPB on peas provided sufficient data to support MCPA. In the metabolism of MCPB in peas (MRID 42966301) MCPB converts to MCPA which is further metabolized to hydroxylated MCPA. This in turn forms a glucose

conjugate and bound residues. This pathway is observed in the metabolic pathway of MCPA in wheat (MRID 43580301). The metabolic pathways of MCPB in peas and MCPA in wheat are illustrated in Appendix A. Metabolic Pathways. In addition, radiolabeled data of MCPB on peas showed the major metabolic products to be MCPA (S. Funk, D207498 and D196282, June 28, 1995). This supported the translation of MCPB metabolism on peas to be used in support of MCPA metabolism on peas and satisfies Guideline 860.1300. Thus, HED concluded that this data deficiency was resolved.

4.1.2 Summary of Confined Rotational Crops (860.1850)

P. Savoia, D417753, June 30, 2014

The MCPA Task Force Three submitted a confined rotational crop study for MCPA during the 2012 through 2013 growing years using representative root (radish), leafy vegetable (lettuce), and grain (wheat) crops planted into sandy loam soil treated beforehand with [^{14}C]-MCPA. Treated rates were equivalent to 1x the maximum seasonal rate for annual crops. The parent MCPA compound as well as its known plant metabolites 2-HMCPA and CCPA (2-carboxy-4-chlorophenoxyacetic acid) were not identified in any rotational crop matrix at any PBI. Although a metabolic pathway for confined rotational crops was not proposed, the petitioner indicated that the extractable portion of the TRR consisted of multiple components which suggest extensive degradation or metabolism of MCPA. Most of the remaining ^{14}C activity was incorporated into non-extractable residues. Based on the extensive metabolism of MCPA, low TRR observed in plant matrices and the absence of residues of concern, a 60-day PBI was determined to be adequate for rotational crops.

4.2 Residues of Concern Summary and Rationale

MARC, D308991, October 7, 2004

The MARC memo (D308991) noted that there was insufficient information to conclude that 2-HMCPA was significantly less toxic than MCPA; it is therefore included in the residue of concern for risk assessment for plants. It was concluded that residues of CCPA are significantly less toxic than MCPA; therefore, the risk contribution from the metabolite CCPA does not need to be included in MCPA assessments. Residues of MCPA will likely be equal to or exceed 2-HMCPA residues, and therefore, would serve as a sufficient marker for tolerance enforcement. For risk assessment, the residue of concern in livestock commodities and drinking water is MCPA.

The residues of concern for tolerance enforcement and risk assessment are presented in Table 4.2.

Table 4.2. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression			
Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	MCPA and 2-HMCPA	MCPA
	Rotational Crop	MCPA and 2-HMCPA	MCPA

Table 4.2. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Livestock	Ruminant	MCPA	MCPA
	Poultry	MCPA	MCPA
Drinking Water		MCPA	Not Applicable

5.0 Residue Profile

5.1 Residue Analytical Methods (860.1340)

5.1.2 Multi-Residue Methods (860.1360)

F. Fort, D307890, September 14, 2004

The PESTRAK database dated 11/01 (PAM Volume I, Appendix I) indicates that the recovery of MCPA is variable (60-131%) using Multiresidue Method 402 (method for acids and phenols) but does not contain any information about the recovery of MCPA (or MCPA methyl ester) through Sections 301, 302, and 303 multiresidue methods.

5.1.3 Tolerance Enforcement Methods

F. Fort, D307890, September 14, 2004

For enforcement of tolerances for residues of MCPA, the Residue Chemistry Chapter of the Registration Standard dated 8/31/81 noted that the PAM Vol. I method was adequate for enforcement of tolerances for residues of MCPA in livestock commodities but recommended that the method be modified with a hydrolysis step for enforcement of MCPA tolerances for plant commodities. The current PAM Vol II methods are adequate for the enforcement of MCPA on plants and livestock commodities and no further modifications are required at this time. The data requirement for 860.1340 residue analytical methods is fulfilled.

5.1.4 Submittal of Analytical Reference Standards (860.1650)

The analytical standard for MCPA (CAS # 94-74-6) are available at the EPA National Pesticide Standards Repository with an expiration date of April 21, 2020 [email communication from G. Verdin, July 19, 2018]. A fresh reference standard can be provided to the Repository, and then replenished as requested by the Repository. The reference standard should be sent to the Analytical Chemistry Lab, which is located at Fort Meade, to the attention of Theresa Cole at the following address:

USEPA
National Pesticide Standards Repository/Analytical Chemistry Branch/OPP
701 Mapes Road
Fort George G. Meade, MD 20755-5350

The full 9 digit zip code is mandatory or the mail will be returned.

5.2 Residue Data

5.2.1 Crop Field Trials (860.1500)

D. Drew, D437360, June 14, 2017
46242401.der

Pea

The MCPA Task Force Three has submitted a crop field trial study reflecting the use of MCPA on dry peas (MRID 50107601; Guideline 860.1500) in response to outstanding residue chemistry data requirements. Review of the recent data showed that residues of MCPA were <0.25-0.60 ppm in pea forage samples and <0.25-0.91 ppm in pea hay samples harvested at various time periods between the pre-pod and the pea-fill stage (PHIs ranged from 14-41 days) following applications approximating the 1x rate (at 0.41-0.43 lb ae/A). These data indicate that the current tolerance of 0.1 ppm for pea hay and vines is too low. Using the Organization for Economic Co-operation and Development (OECD) calculation procedure for these results, a tolerance level of 0.60 ppm for pea vines and 1.5 ppm for pea hay is now being recommended (D. Drew, D437360, June 14, 2017).

In addition, these data showed that residues of MCPA in dry pea were <0.010 ppm following applications approximating the 1x rate (MRID 50107601; Guideline 860.1500). These data indicate that the current tolerance of 0.1 ppm for pea, dry is too high and a tolerance at the method LOQ of 0.01 ppm is recommended and is harmonized with Codex MRL.

Flax

The IR-4 has submitted a crop field trail study reflecting the use of MCPA on flax (MRID 46242401; Guideline 860.1500) in response to outstanding residue chemistry data requirements. Review of the recent data showed that residues of MCPA were <0.025 ppm following applications approximating the 1x and 2x rate (at 0.25 and 0.50 lbs ai/A). These data indicate that the current tolerance of 0.1 ppm for flax, seed is too high (see 46242401.der). A tolerance level of 0.01 ppm based on Codex MRLs for flax, seed is now being recommended.

5.2.2 Meat, Milk, Poultry and Eggs (860.1480)

47075201.der

Currently there are no registered direct livestock treatments of MCPA. However, MCPA is registered for use on several livestock feed items. MCPA Task Force Three has submitted cattle feeding study in which three groups of dairy cows were dosed orally with MCPA in gelatin capsules, once daily for 28 days at doses equivalent to 50, 150, and 500 ppm MCPA. Samples of milk, cream, and tissues were analyzed for residues of MCPA using a gas chromatography with mass selective detection (GC-MSD) method with limits of quantitation of 0.010 ppm for milk and 0.050 ppm for tissues. Acceptable method validation and concurrent recoveries were obtained for samples fortified with MCPA. The study author reported that the storage stability study encompassed the maximum storage duration of samples from the feeding study. Freezer storage stability data were generated concurrently with the livestock feeding study and showed that MCPA residues were stable in cow milk and tissues under frozen storage for up to 120 days

in milk, 112 days in muscle, 134 days in liver, 153 days in kidney, and 173 days in fat.

MCPA residues increased with increasing feeding levels in liver, but were consistent or declined in the 150 ppm and 500 ppm dose groups for fat and muscle. Residues of MCPA were highest in kidney and increased with increasing feeding levels. Residues of MCPA in whole milk samples were below LOQ for the 50 ppm and 150 ppm dose groups while the 500 ppm dose group ranged from <0.010-0.043 ppm. Cream MCPA residues collected from the 500 ppm dose group were 0.015-0.020 ppm. A summary of the feeding results and the calculated residue tissue to feed ratio is provided in the table below.

Table 5.2.2. Summary of Livestock Feeding Studies with MCPA.				
Commodity	Feeding Level, ppm	Median Residue, ppm	Maximum Residue, ppm ¹	Transfer coefficient (TC) ³
Whole Milk	50.3	0.010	<0.010	NC
	151.2	0.010	<0.010	NC
	504.7	0.018	0.043	<0.001
Cream	504.7	0.017	0.020	<0.001
Muscle (cattle)	50.3	0.050	<0.050	NC
	151.2	0.050	0.077	0.001
	504.7	0.051	0.076	<0.001
Fat (cattle) ²	50.3	0.050	<0.050	NC
	151.2	0.119	0.172	0.001
	504.7	0.116	0.133	<0.001
Liver (cattle)	50.3	0.050	<0.050	NC
	151.2	0.058	0.095	0.001
	504.7	0.246	0.282	0.001
Kidney (cattle)	50.3	0.400	0.410	0.008
	151.2	0.627	1.20	0.008
	504.7	0.169	2.44	0.005

¹ Maximum residue.

² Composite of omental, subcutaneous, or perirenal

³ NC- not calculated; all residues were at or below the LOQ

5.2.2.1 Dietary Burden

With new MCPA residue tissue transfer coefficients HED updated the dietary burdens of livestock according to OECD methods. The Dietary Burden Calculator PMRA v.2.8 was used to determine the More Balanced Diets (MBDs), which is based on the Guidance Document on Residues in Livestock, 04-SEP-2013 (OECD ENV/JM/MONO(2013)8). Table 5.2.2.1 summarizes the MCPA MBDs total dietary contributions for beef and dairy cattle, poultry, and swine.

Table 5.2.2.1 More Balanced Diet (MBD)							
Crop	Commodity	Type	Residue		%DM	%Diet	Dietary Contribution
			ppm	input			
Beef Cattle							
Grass	Hay	R	217	HAFT	88	15	36.99
Grain	Aspirated grain fractions	CC	3	Median	85	5	0.18
Barley	Grain	CC	0.279	Median	88	50	0.16
Rye	Grain	CC	0.279	Median	88	20	0.06

Wheat	Grain	CC	0.279	Median	89	5	0.02
Untreated feed	NA	NA	NA	NA	NA	5	0
Total	NA	NA	NA	NA	NA	100	37.4
Dairy Cattle							
Grass	Forage	R	108	HAFT	25	45	194.40
Barley	Grain	CC	0.279	Median	88	45	0.14
Untreated feed	NA	NA	NA	NA	NA	10	0
Total	NA	NA	NA	NA	NA	100	194.54
Poultry							
Barley	Grain	CC	0.279	Median	88	75	0.21
Pea, field	Seed	PC	0.19	Median	90	20	0.04
Untreated feed	NA	NA	NA	NA	NA	5	0
Total	NA	NA	NA	NA	NA	100	0.25
Swine							
Barley	Grain	CC	0.279	Median	88	20	0.06
Pea, field	Seed	PC	0.19	Median	90	15	0.03
Untreated feed	NA	NA	NA	NA	NA	65	0
Total	NA	NA	NA	NA	NA	100	0.08

¹ R: Roughage; CC: Carbohydrate concentrate; PC: Protein concentrate.

² Table 1 Feedstuffs (July 2008).

³ Contribution = ([tolerance /% DM] X % diet) for beef and dairy cattle; contribution = ([tolerance] X % diet) for poultry and swine.

5.2.2.2 Estimated Secondary Residues in Livestock

Estimated secondary residues were calculated by interpolation between the 151.2 ppm and 504.7 ppm feeding level transfer coefficients (Table 5.2.2.2) to the estimated dietary burden of 194.54 ppm (Table 5.2.2.1).

Table 5.2.2.2. Estimation of Secondary Residues from Use of MCPA.			
Commodity	Transfer Coefficient (TC) ¹	Dietary Burden (ppm)	Expected Residue (ppm)
Milk	0.00007	194.54	0.014
Muscle (cattle)	0.0004		0.08
Fat (cattle)	0.0009		0.17
Liver (cattle)	0.0006		0.12
Kidney (cattle)	0.007		1.36

¹ $TC @ 194.54 \text{ ppm} = \frac{TC @ 504.7 \text{ ppm} (504.7 - 151.2) + TC @ 151.2 \text{ ppm} (194.54 - 151.2)}{504.7 - 151.2}$

Conclusions.

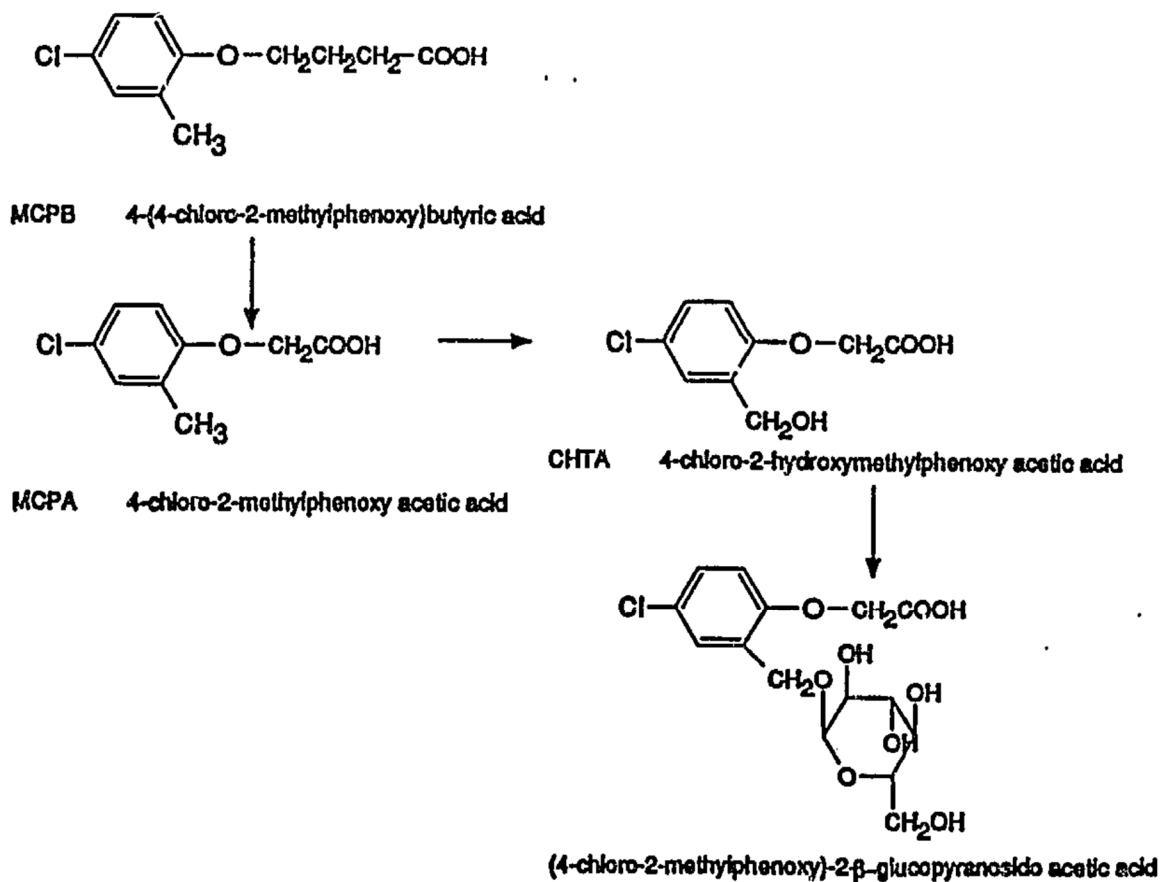
Based upon the Maximum Reasonably Balanced Diet, tolerances for ruminant commodities are required. Previous tolerances set at 0.1 ppm for ruminant fat, liver, and kidney are too low and should be increased to 0.20 ppm for fat, and 3.0 ppm for kidney and liver to account for the updated livestock dietary burdens and to harmonize with Codex MRLs. Milk tolerances are currently too high and should be lowered from 0.1 ppm to 0.04 ppm to correct for new data and to harmonize with Codex MRLs. Ruminant muscle tolerance (0.10 ppm) is at an acceptable level. Poultry and swine commodities are not expected to yield quantifiable residues and therefore a Category 3 of 40 CFR §180.6(a) situation exists.

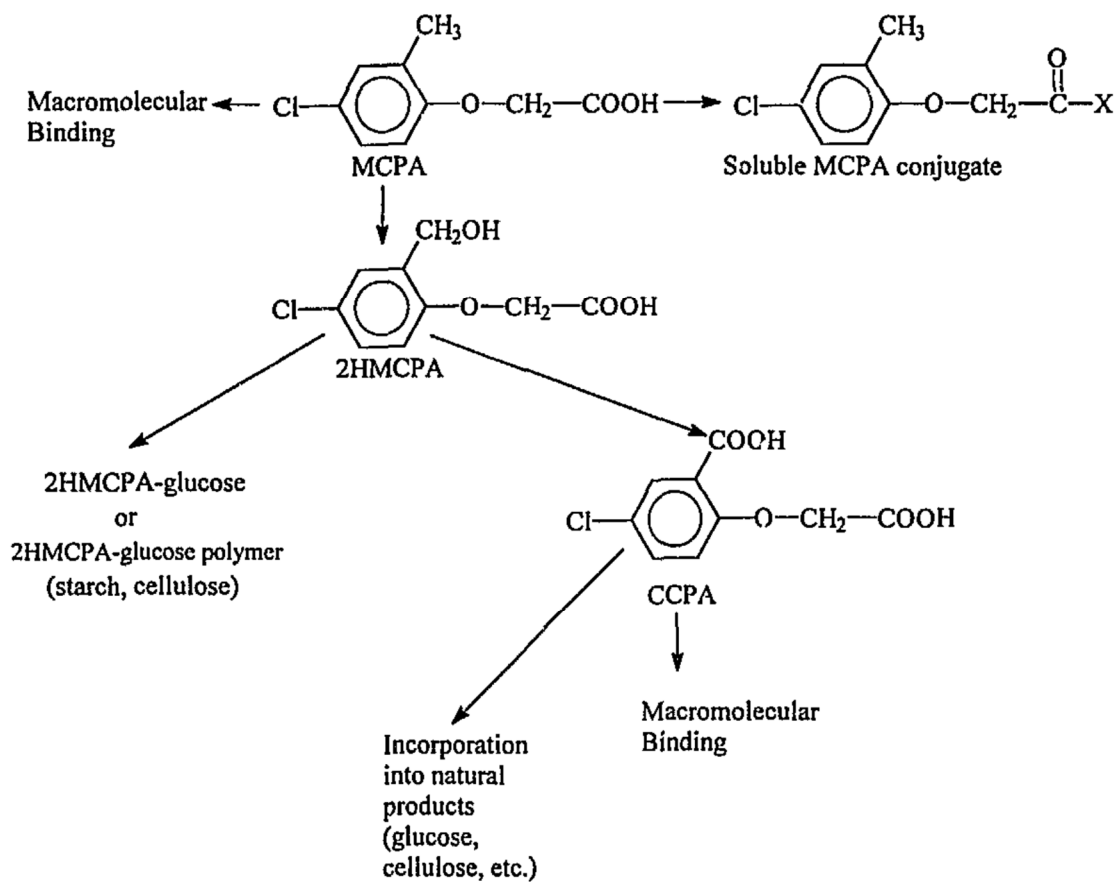
5.3 Food Residue Profile

Tolerances are established in the 40 CFR §180.339 for the residues of MCPA on alfalfa, barley, flax, oat, rye, and wheat. In addition, tolerances are established for ruminant livestock commodities, and several feed commodities. Tolerances range from 0.01 ppm (flax) to 500 ppm (grass, hay). Generally, residues below 0.20 ppm are expected in most food commodities except for ruminant meat byproducts (3.0 ppm). Several tolerances were updated as part of this action to use the latest available information and to harmonize with Codex. Food commodities updated include barley, oat, rye, and wheat grains were reduced from 1.0 ppm to 0.20 ppm and flax, seed was reduced from 1.0 ppm to 0.01 ppm. In addition, the livestock dietary burden was recalculated to determine new tolerances for livestock commodities. These updated calculations lowered the tolerance for milk 0.1 ppm to 0.04 ppm, remained the same for ruminant meat 0.10 ppm, and were increased for ruminant fat 0.1 ppm to 0.20 ppm and ruminant meat byproducts 0.1 ppm to 3.0 ppm. the available residue chemistry data are adequate for establishing appropriate tolerance levels for enforcement, and for purposes of risk assessment.

Appendix A. Metabolic Pathways

MCPB: Metabolic Pathway in Peas



MCPA: Metabolic Pathway in Wheat

Appendix B. International Residue Limits Table

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico ²	Codex
40 CFR 180.339: <i>Compliance with the tolerance levels specified below is to be determined by measuring only MCPA, 2-(4-chloro-2-methylphenoxy)acetic acid, in or on the commodity</i>		<i>MCPA: 2-(4-chloro-2-methylphenoxy)acetic acid</i>		<i>MCPA</i>
Commodity ¹	Tolerance (ppm) /Maximum Residue Limit (mg/kg)			
	US	Canada	Mexico ²	Codex ³
Alfalfa, forage	0.50			
Alfalfa, hay	2.0			
Barley, grain	0.20	0.03		0.2
Barley, hay	50			50
Barley, straw	50			50
Clover, forage	0.50			
Clover, hay	2.0			
Corn, grain		0.01		0.01*
Corn, sweet		0.015		
Poultry, byproducts		0.05		0.05*
Poultry, fat		0.05		0.05*
Poultry, meat		0.05		0.05*
Eggs		0.05		0.05*
Flax, seed	0.01	0.01		0.01*
Grain, aspirated fractions	3.0			
Grass, forage	500			500
Grass, hay	200			
Hog, byproducts		0.05		3
Hog, fat		0.05		0.2
Hog, meat		0.05		0.1
Lespedeza, forage	0.50			
Lespedeza, hay	2.0			
Milk	0.04	0.01		0.04
Oat, forage	50			50
Oat, grain	0.20	0.03		0.2
Oat, hay	50			50
Oat, straw	50			50
Pea, dry	0.01	0.1		0.01*
Pea, field, hay	1.5			
Pea, succulent	0.10	0.1		
Pea, field, vines	0.60			
Ruminant, meat by products	3.0	0.05		3

Summary of US and International Tolerances and Maximum Residue Limits				
<i>Residue Definition:</i>				
US		Canada	Mexico ²	Codex
Ruminant, fat	0.20	0.05		0.2
Ruminant, meat	0.10	0.05		0.1
Rye, forage	50			50
Rye, grain	0.20	0.03		0.2
Rye, straw	50			50
Trefoil, forage	0.50			
Trefoil, hay	2.0			
Triticale, grain†	0.50			0.2
Triticale, straw†	2.0			50
Vetch, forage	0.50			
Vetch, hay	2.0			
Wheat, forage	50			50
Wheat, grain	0.20	0.03		0.2
Wheat, hay	50			50
Wheat, straw	50			50
Completed: D. Nadrchal 7/24/18				

¹ Tolerance values are the HED recommendations and not those proposed by the applicant.

² Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

³ *Codex additional description of “At or about the limit of determination”

† Wheat commodity definition in CFR 180.1 (g) includes triticale

[illegible]

Compound	MCPA	MCPA																																																																		
Crop	Wheat, Grain	Wheat, Grain																																																																		
Region / Country	USA	USA																																																																		
GAP	Immature (PHI 30-31 Days)	Mature (PHI 63-93 days)																																																																		
Total number of data (n)	15	15																																																																		
Percentage of censored data	53%	93%																																																																		
Number of non-censored data	7	1																																																																		
Lowest residue	0.010	0.010																																																																		
Highest residue	0.142	0.011																																																																		
Median residue	0.010	0.010																																																																		
Mean	0.023	0.010																																																																		
Standard deviation (SD)	0.034	0.000																																																																		
Correction factor for censoring (CF)	0.644	0.378																																																																		
<u>Proposed MRL estimate</u>																																																																				
- Highest residue	0.142	0.011																																																																		
- Mean + 4 SD	0.159	0.011																																																																		
- CF x 3 Mean	0.044	0.011																																																																		
Unrounded MRL	0.159	0.011																																																																		
Rounded MRL	0.2	0.015																																																																		
	High uncertainty of MRL estimate due to high level of censoring.	High uncertainty of MRL estimate due to high level of censoring.																																																																		
	<table><tr><th colspan="2">Residues (mg/kg)</th></tr><tr><td>0.010</td><td>*</td></tr><tr><td>0.040</td><td></td></tr><tr><td>0.032</td><td></td></tr><tr><td>0.010</td><td>*</td></tr><tr><td>0.015</td><td></td></tr><tr><td>0.010</td><td>*</td></tr><tr><td>0.010</td><td></td></tr><tr><td>0.142</td><td></td></tr><tr><td>0.010</td><td>*</td></tr><tr><td>0.013</td><td></td></tr><tr><td>0.010</td><td>*</td></tr><tr><td>0.010</td><td>*</td></tr><tr><td>0.010</td><td>*</td></tr><tr><td>0.010</td><td>*</td></tr><tr><td>0.010</td><td>*</td></tr><tr><td>0.014</td><td></td></tr></table>	Residues (mg/kg)		0.010	*	0.040		0.032		0.010	*	0.015		0.010	*	0.010		0.142		0.010	*	0.013		0.010	*	0.010	*	0.010	*	0.010	*	0.010	*	0.014		<table><tr><th colspan="2">Residues (mg/kg)</th></tr><tr><td>0.010</td><td>*</td></tr><tr><td>0.010</td><td>*</td></tr><tr><td>0.010</td><td>*</td></tr><tr><td>0.010</td><td>*</td></tr><tr><td>0.010</td><td>*</td></tr><tr><td>0.010</td><td>*</td></tr><tr><td>0.010</td><td>*</td></tr><tr><td>0.010</td><td>*</td></tr><tr><td>0.011</td><td></td></tr><tr><td>0.010</td><td>*</td></tr><tr><td>0.010</td><td>*</td></tr><tr><td>0.010</td><td>*</td></tr><tr><td>0.010</td><td>*</td></tr><tr><td>0.010</td><td>*</td></tr><tr><td>0.010</td><td>*</td></tr></table>	Residues (mg/kg)		0.010	*	0.010	*	0.010	*	0.010	*	0.010	*	0.010	*	0.010	*	0.010	*	0.011		0.010	*	0.010	*	0.010	*	0.010	*	0.010	*	0.010	*
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Compound	MCPA	MCPA
Crop	Wheat, Hay	Wheat, Hay
Region / Country	USA	USA
GAP	PHI 7 Days (2x label rate)	PHI 7 Days (corrected to ≈1x label rate)
Total number of data (n)	15	15
Percentage of censored data	0%	0%
Number of non-censored data	15	15
Lowest residue	7.180	3.590
Highest residue	52.150	26.075
Median residue	12.450	6.225
Mean	17.356	8.678
Standard deviation (SD)	12.298	6.149
Correction factor for censoring (CF)	1.000	1.000
<u>Proposed MRL estimate</u>		
- Highest residue	52.150	26.075
- Mean + 4 SD	66.547	33.273
- CF x 3 Mean	52.069	26.035
Unrounded MRL	66.547	33.273
Rounded MRL	<u>70</u>	<u>40</u>
	Residues (mg/kg)	Residues (mg/kg)
	36.200	18.100
	9.645	4.823
	16.000	8.000
	10.525	5.263
	14.750	7.375
	52.150	26.075
	12.450	6.225
	21.500	10.750
	10.265	5.133
	15.900	7.950
	24.900	12.450
	8.235	4.118
	10.830	5.415
	7.180	3.590
	9.815	4.908

**B.7.6 Residues Resulting from Supervised Trials
(Annex IIA 6.3; Annex IIIA 8.3)**

B.7.6.1 Residues in Target Crops

B.7.6.1.1 Flax

Document ID: MRID No. 46242401
PMRA No.: NA
Report: Report Citation
Guidelines: EPA OCSPP Harmonized Test Guideline 860.1500 Crop Field Trials
(August 1996)
PMRA Regulatory Directive DIR98-02 – Residue Chemistry Guidelines,
Section 9 – Crop Field Trials
PMRA Regulatory Directive DIR2010-05 – Revisions to the Residue
Chemistry Crop Field Trial Requirements
OECD Guideline 509 Crop Field Trial (September 2009)
GLP Compliance: No significant deviations from regulatory requirements were reported
which would have an impact on the validity of the study
Acceptability: The study is considered scientifically acceptable.
Evaluator: David Nadrchal, Chemist, US EPA



EXECUTIVE SUMMARY

Five field trials for MCPA on flax seed were conducted in the United States encompassing North American Free Trade Agreement (NAFTA) Growing Region 7 during the 1996 growing season.

At each trial location, the treated plots one time rate of approximately 0.25 (1x max label rate) and 0.50 (2x max label rate) lb ai/A using MCPA Amine and MCPA ester formulations. One emergence, foliar broadcast application was made when flax plants were approximately 8 inches tall. Applications were made with appropriate spray equipment. An adjuvant was not added to the spray mixture for all applications. Flax seed were harvested at a preharvest interval (PHI) of 58-100 days.

All samples were maintained frozen at the testing facility, during shipping to the laboratory, and were stored frozen until analysis. The maximum storage interval for samples between harvest and analysis was 1255 days. Residues of MCPA have been shown to be stable in flax for up to 1205 days under frozen conditions. Adequate storage stability data are therefore available to support the storage conditions and intervals for samples in the current trials.

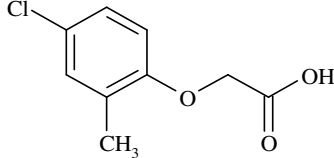
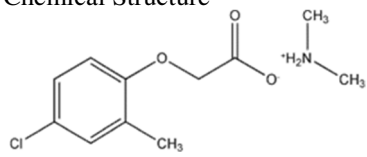
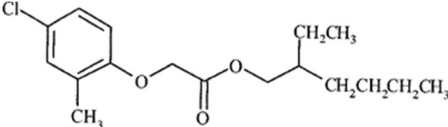
Samples in the current study were analyzed using Method Covance Study No 6698-107, a “Determination of 4-chloro-2-methylphenoxyacetic acid, 2-ethylhexyl ester (MCPA 2-EHE) and 4-chloro-2-methylphenoxyacetic acid dimethylamine salt (MCPA DMAS) as their 4-chloro-2-methylphenoxyacetic acid (MCPA) equivalent, MCPA, 4-chloro-2-hydroxymethylphenoxyacetic acid (HMCPA), 4-chloro-2-hydroxymethylphenoxyacetic acid glucose conjugate (HMCPA

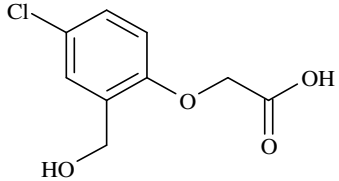
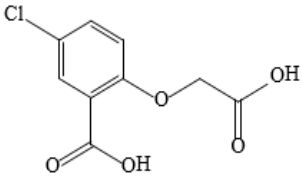
GLU) as its HMCPA equivalent, and 4-chlorocarboxyphenoxy acetic acid (CCPA) in Wheat Forage and Hay Samples by Gas Chromatography with Mass Selective Detection (GC-MSD) to determine residues of MCPA, 2-HMCPA, and CCPA”. Acceptable concurrent recoveries were reported for flax samples at fortification levels of 0.025 mg/kg (ppm), thus validating the method. The limit of quantitation (LOQ) was 0.025 ppm per analyte for flax, seed.

Individual sample (and per-trial average) residues in flax, seed for MCPA and metabolites were all below the method LOQ (0.025 ppm).

I. MATERIALS AND METHODS

A. MATERIALS

Table B.7.6.1.1-1. Nomenclature for MCPA and Metabolites of Interest.	
Compound	Chemical Structure 
Common name	MCPA
IUPAC name	4-chloro-o-tolyloxyacetic acid
CAS name	2-(4-chloro-2-methylphenoxy)acetic acid
CAS #	94-74-6
PC Code	030501
Compound	Chemical Structure 
Common name	MCPA dimethylamine salt (DMA)
IUPAC name	(4-chloro-2-methylphenoxy)acetic acid, dimethylamine salt
CAS name	(4-chloro-2-methylphenoxy)acetic acid, compound with N-methylmethanamine (1:1)
CAS #	2039-46-5
PC Code	030516
Compound	Chemical Structure 
Common name	MCPA 2-ethylhexyl ester (2-EHE)
IUPAC name	2-ethylhexyl 2-(4-chloro-2-methylphenoxy)acetate
CAS name	(4-chloro-2-methylphenoxy)acetic acid, 2-ethylhexyl ester
CAS #	29450-45-1
PC Code	030564

Metabolite	Chemical Structure 
Common name	2-HMCPA
IUPAC name	4-chloro-2-hydroxymethylphenoxyacetic acid
CAS name	
CAS #	
Metabolite	Chemical Structure 
Common name	CCPA
IUPAC name	(4-chlorophenoxy)acetic acid
CAS name	2-carboxy-4-chlorophenoxyacetic acid
CAS #	122-88-3

B. Study Design

1. Test Procedure

A total of 5 residue trials in/on flax, seed were conducted with a [formulation] during the 1996 and 1997 growing season(s) (Table B.7.6.1.1-2).

Table B.7.6.1.1-2. Trial Numbers and Geographical Locations.															
Crop	Region														Total
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Flax, Seed							5								5
Flax, Meal							5								5

Locations and detailed use patterns for the trials are provided in Table B.7.6.1.1-3.

Table B.7.6.1.1-3. Study Use Pattern.							
Location: City, State/Province; Year (Trial ID)	End-use Product/ Formulation (% ai)	Method of Application/ Timing of Application	Volume (gal/A)	Rate per Application (lbs ai/A)	Retreatment Interval (days)	Total Rate (lbs ai/A)	Surfactant/ Adjuvant
Fargo, ND 1996 (05000.96-ND06)	MCPA Amine	Foliar broadcast/Crop height 8 inches	7.76	0.25	NA	0.25	None
			7.70	0.50		0.50	
	MCPA Ester		7.75	0.25		0.25	
			7.81	0.507		0.507	
Fargo, ND 1996 (05000.96-ND07)	MCPA Amine		7.94	0.257		0.257	
			7.81	0.508		0.508	
	MCPA Ester		7.75	0.25		0.25	

Table B.7.6.1.1-3. Study Use Pattern.							
Location: City, State/Province; Year (Trial ID)	End-use Product/ Formulation (% ai)	Method of Application/ Timing of Application	Volume (gal/A)	Rate per Application (lbs ai/A)	Retreatment Interval (days)	Total Rate (lbs ai/A)	Surfactant/ Adjuvant
Aurora, SD 1996 (05000.96-SD03)	MCPA Amine	Foliar broadcast/Crop height 8-9 inches	7.84	0.510		0.510	
			12.92	0.19		0.19	
			16.99	0.50		0.50	
			15.93	0.23		0.23	
			16.99	0.50		0.50	
Fargo, ND 1997 (05000.97-ND04)	MCPA Amine	Foliar broadcast/Crop height 9 inches	7.7	0.25		0.25	
			7.87	0.506		0.506	
			7.96	0.256		0.256	
			7.83	0.510		0.510	
Aurora, SD 1997 (05000.97-SD05)	MCPA Amine	Foliar broadcast/Crop height 10 inches	19.14	0.25		0.25	
			19.14	0.50		0.50	
			19.14	0.25		0.25	
			19.14	0.50		0.50	
	MCPA Ester						

Flax were grown and maintained according to typical agricultural practices. Irrigation was not used. Weather conditions were reported during the study were normal or cooler than average.

Sample Handling and Preparation

Duplicate samples of marketable flax seed were collected from the plots treated with 0.25 and 0.50 lb ai/A. Each fresh seed flax sample weighed approximately 2-3 lbs, each flax seed for meal sample weighed approximately 10- 12 lbs and each meal sample weighed approximately 2-4 lbs. All samples were collected in a manner to assure a representative, impartial sample. Samples were placed in residue bags and transferred to a freezer for storage or hand delivered to the laboratory.

Samples from 96-SD03 field site were stored frozen within 2 hours of collection, and shipped frozen via ACDS to the North Dakota IR-4 Satellite analytical laboratory. Samples from 96-ND06 and ND07 field sites were hand delivered fresh to the North Dakota analytical laboratory where they were frozen. Flax meal was prepared on 11/06/1996 at the ND satellite lab. Meal was stored in glass jars with aluminum foil lined lids and frozen.

All 1996 trial samples were kept frozen at the North Dakota IR-4 Satellite Laboratory and then shipped by ACDS on 12/04/1996. All samples were received frozen and in good condition by the Tifton, GA laboratory on 12/12/1996.

After the harvest, samples from 97-ND04 and 97-SD05 field sites were frozen and shipped by ACDS to Tifton, GA laboratory. All flax samples were kept frozen and stored at Tifton, GA laboratory facility until they were transferred to Davis, CA by the ACDS truck on 04/12/1999.

Samples arrived in good frozen condition at IR-4 Western Region Leader Laboratory, Department of Environmental Toxicology, University of California, Davis, CA. All samples were assigned unique sample numbers and stored frozen ($-20 \pm 6^{\circ}\text{C}$) until sample preparation. Sample preparation and analyses took place between May 11, 1999 and March 1, 2000.

Storage stability samples were prepared by the North Dakota Laboratory. On November 5, 1996, 25 gr portions of each matrix from untreated controls were prepared. Six jars for each matrix was fortified with each compound of interest at the 0.10 ppm level. The jars were sealed and frozen. Three stability study samples for each matrix and each compound were analyzed. Remaining stability samples were held for long term archive.

2. Description of Analytical Procedures

Samples of flax, seed were analyzed for residues of MCPA, HMCPA, and CCPA using the Analytical Method Covance Study No.6698-107, "Determination of 4-chloro-2-methylphenoxyacetic acid, 2-ethylhexyl ester (MCPA 2-EHE) and 4-chloro-2-methylphenoxyacetic acid dimethylamine salt (MCPA DMAS) as their 4-chloro-2-methylphenoxyacetic acid (MCPA) equivalent, MCPA, 4-chloro-2-hydroxymethylphenoxyacetic acid (HMCPA), 4-chloro-2-hydroxymethylphenoxyacetic acid glucose conjugate (HMCPA GLU) as its HMCPA equivalent, and 4-chlorocarboxyphenoxy acetic acid (CCPA) in Wheat Forage and Hay Samples by Gas Chromatography with Mass Selective Detection".

Briefly, samples were extracted with acid hydrolysis, oil and ether partitioning with a final derivatization step using 10% sulfuric acid/methanol. Extracts were cleaned up using Florisil columns and a portion of this extract was analyzed for residues of MCPA, HMCPA, and CCPA using gas chromatograph/mass selective detector (GC/MSD). The LOQ was 0.025 ppm for each analyte.

II. RESULTS AND DISCUSSION

Method performance was evaluated during method validation and by use of concurrent recovery samples by fortifying flax seed at 0.025 and 0.10 ppm with MCPA amine, MCPA ester and the metabolites HMCPA and CCPA. Recoveries for MCPA ester were 78% to 83% at 0.025 ppm and 63% to 68% at 0.10 ppm. MCPA amine was 108 % to 116% at 0.025 ppm and 83% to 95% at 0.10 ppm. 16 samples of flax seed were fortified at 0.025 ppm and individual recoveries ranged from 79% to 83% with a standard deviation of 23.98%. Recoveries of MCPA and metabolites HMCPA and CCPA were within the acceptable range of 70% to 120%; therefore, the method was considered valid for the analysis of MCPA, HMCPA and CCPA residues in flax matrices. The fortification levels did not bracket the measured residues.

The detector response was linear (coefficient of determination, $r^2 > 0.998$) within the range of 0.005 ppm to 0.20 ppm. Representative chromatograms of control samples, fortified samples and treated samples were provided. The control chromatograms generally had no peaks of interest above the chromatographic background. The fortified sample chromatograms contained only the analyte of interest, and peaks were symmetrical and well defined.

The field residue samples were stored frozen a maximum of 1212 days from harvest to analysis (Table B.7.6.1.1-5). Freezer storage stability data were generated concurrently with the flax field trials. Data showed that MCPA, HMCPA and CCPA residues were stable in flax seed and flax meal under frozen storage for the duration of the storage period.

Table B.7.6.1.1-5. Summary of Storage Conditions.			
Matrix (RAC or Extract)	Storage Temperature (°C)	Actual Storage Duration (days/months)	Interval of Demonstrated Storage Stability (days/months)
Flax, Seed	-20	1207 days	1256 days
Flax, Meal		1212 days	1241 days

The results from these trials showed that when harvested 58-100 days after application at a seasonal rate of 0.25 and 0.50 lbs ai/A, residues of MCPA, HMCPA and CCPA in flax, seed ranged were less than method LOQ (0.025 ppm) (Tables B.7.6.1.1-6). Due to the very low levels of observed residues, no decline trend could be determined in flax.

Table B.7.6.1.1-6. Residue Data from Flax Field Trials with MCPA									
Location: City, State/Province; Year (Trial ID)	Region	Crop/ Variety	Matrix	End-Use Product	Rate (lbs ai/A)	PHI (days)	Residues ¹ (ppm)		
							MCPA	HMCPA	CCPA
Fargo, ND; 1996 (96-ND06)	7	Flax	Seed	MCPA	0.25	100	<0.025	<0.025	<0.025
				Amine	0.50		<0.025	<0.025	<0.025
				MCPA	0.25		<0.025	<0.025	<0.025
				Ester	0.507		<0.025	<0.025	<0.025
Prosper, ND; 1996 (96-ND07)	7	Flax	Seed	MCPA	0.257	71	<0.025	<0.025	<0.025
				Amine	0.508		<0.025	<0.025	<0.025
				MCPA	0.25		<0.025	<0.025	<0.025
				Ester	0.51		<0.025	<0.025	<0.025
Aurora, SD; 1996 (96-SD03)	7	Flax	Seed	MCPA	0.19	63	<0.025	<0.025	<0.025
				Amine	0.50		<0.025	<0.025	<0.025
				MCPA	0.23		<0.025	<0.025	<0.025
				Ester	0.50		<0.025	<0.025	<0.025
Fargo, ND; 1997 (97-ND04)	7	Flax	Seed	MCPA	0.25	90	<0.025	<0.025	<0.025
				Amine	0.506		<0.025	<0.025	<0.025
				MCPA	0.256		<0.025	<0.025	<0.025
				Ester	0.510		<0.025	<0.025	<0.025
Aurora, SD; 1997 (97-SD05)	7	Flax	Seed	MCPA	0.25	58	<0.025	<0.025	<0.025
				Amine	0.50		<0.025	<0.025	<0.025
				MCPA	0.25		<0.025	<0.025	<0.025
				Ester	0.50		<0.025	<0.025	<0.025

¹ Expressed as parent equivalents.

III. CONCLUSIONS

The flax field trials are considered scientifically acceptable. The results of the study showed that following a total application of 0.25 lb ai/A in flax samples collected at PHIs of 58-100 days, MCPA and metabolites HMCPA and CCPA residues were below method LOQs (0.025 ppm). Adequate storage stability data are available to support sample storage durations and conditions.

DATA EVALUATION RECORD

MCPA

Study Type: OCSPP 860.1480, Meat/Milk/Poultry/Eggs

EPA Contract No. EP-W-16-018

Task Assignment Form No. 21-2-007 (MRID 47075201)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

Prepared by



3201 Jermantown Rd., Suite 400
Fairfax, VA 22030

Primary Reviewer:

Sandra Hastings

Signature: *Sandra Hastings*

Date: 11/21/17

Secondary Reviewer:

Tara K. B. Johnson, M.A.T.

Signature: *Tara K. B. Johnson*

Date: 11/27/17

Quality Assurance:

Jack D. Early, M.S.

Signature: *Jack D. Early*

Date: 11/28/17

Project Manager:

Jack D. Early, M.S.

Signature: *Jack D. Early*

Date: 11/28/17

**B.7.8 Livestock Feeding Studies
(Annex IIA 6.4; Annex IIIA 8.4)**

B.7.8.1 Cattle


Document ID: MRID No. 47075201
PMRA No. NA

Report: Koch, D.A. (2007) Magnitude of Residues of MCPA in Dairy Cow Milk and Tissues. Study Numbers: 49737; 214-001-10. Unpublished study prepared by ABC Laboratories, Inc. and submitted by MCPA Task Force Three. 279 p.

Guidelines: EPA OCSPP Harmonized Test Guideline 860.1480
Meat/Milk/Poultry/Eggs (August 1996)
PMRA Regulatory Directive DIR98-02 – Residue Chemistry Guidelines, Section 8 – Meat/Milk/Poultry/Eggs
OECD Guideline 505 Residues in Livestock (January 2007)

GLP Compliance: No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

Acceptability: The study is tentatively considered scientifically acceptable pending submission of the raw analytical data and study dates. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document, DP# 448530.

Evaluator: David Nadrchal, Chemist, US EPA 

Note: This Data Evaluation Record (DER) was originally prepared under contract by CDM/CSS-Dynamac Joint Venture (3201 Jermantown Rd., Suite 400, Fairfax, VA 22030; submitted 11/28/17). The DER has been reviewed by HED and revised as necessary to reflect current Office of Pesticide Programs (OPP) policies.

EXECUTIVE SUMMARY

MCPA Task Force Three has submitted a cattle feeding study in which three groups of dairy cows (3 cows/group) were dosed orally with MCPA in gelatin capsules, once daily after the morning milking for 28 days, at doses equivalent to ~50, 150, and 500 ppm MCPA in the diet on a dry-weight basis. Three additional cows were dosed at 500 ppm for 28 days and then were not dosed for 7 days to obtain depuration data. One group of three control cows received gelatin capsules without MCPA, one control cow for the main study and two for the depuration study. The in-life phase of the study was conducted by Genesis Midwest Laboratories (Neillsville, WI), and the analytical phase was conducted by ABC Laboratories, Inc. (Columbia, MO).

Cows were milked twice daily (evening and the following morning prior to dosing), and composited daily samples for each cow were collected each day; whole milk samples from Study Days 0, 1, 3, 7, 11, 14, 18, 21, 24, and 27 from the control and 500-ppm groups were analyzed, and whole milk samples from Study Days 1, 7, 14, and 27 from the 50- and 150-ppm dose groups were analyzed. In addition, milk was collected from the depuration cows on Study Days 29 and 30. Extra milk samples collected on Study Day 27 from the control and high-dose groups were centrifuged to generate separate skim milk and cream samples; only cream samples were analyzed. Animals that were not included in the depuration study were sacrificed on Day 29,

within 24 hours after the final dose on Day 28. For the depuration study, the remaining two control and three 500-ppm group cows were terminated on Study Day 36 (8 days post-dose). Samples of liver, kidney, muscle (composite of round, flank, and loin), and fat (composite of omental, perirenal, and subcutaneous) were collected from each cow.

All samples were maintained frozen at the in-life facility, during shipping, and at the analytical laboratory prior to analysis. Storage durations for samples between collection and extraction for analysis were not reported; extraction and analysis dates (or raw data) were not provided to independently determine maximum sample storage durations. However, freezer storage stability data were generated concurrently with the livestock feeding study. These data showed that MCPA residues were stable in cow milk and tissues under frozen storage for up to 120 days in milk, 112 days in muscle, 134 days in liver, 153 days in kidney, and 173 days in fat. The study author reported that the storage stability study encompassed the storage durations of samples from the feeding study; however, study dates are required to confirm the storage durations for the feeding study samples.

Samples of milk, cream, and tissues were analyzed for residues of MCPA using a gas chromatography with mass selective detection (GC/MSD) method adapted from PTRL Report No. 1905 for the analysis of 2,4-Dichlorophenoxybutyric Acid (2,4-DB). MCPA was determined as the methyl ester and reported as MCPA acid equivalents; the methyl ester standards were prepared as MCPA equivalents. The limits of quantitation (LOQs; determined as the lowest level of method validation, LLMV) were 0.010 ppm for milk and 0.050 ppm for tissues. Acceptable method validation and concurrent recoveries were obtained for samples fortified with MCPA at 0.01-0.1 ppm for milk, 0.01 and 0.05 ppm for cream, 0.05 and 0.5 ppm for fat, liver, and muscle, and 0.05-5.0 ppm for kidney. The fortification levels bracketed the measured residue levels.

Residues of MCPA were below the LOQ (<0.010 ppm) in all whole milk samples from the 50- and 150-ppm dose groups throughout dosing. Residues of MCPA in whole milk samples from the 500-ppm dose group were <0.010-0.043 ppm and relatively consistent over time (Days 1-27). Skim milk was not analyzed, but in cream collected on Day 27 from three 500-ppm dosed cows, residues of MCPA were 0.015-0.020 ppm and similar to the corresponding residues in whole milk (0.013-0.022 ppm).

Following 28 days of dosing, MCPA residues were below the LOQ (<0.050 ppm) in fat, liver, and muscle samples from the 50-ppm dose group. In samples from the 150- and 500-ppm dose groups, residues of MCPA were, respectively, <0.050-0.172 and <0.050-0.133 ppm in fat; <0.050-0.095 and 0.160-0.282 ppm in liver; and <0.050-0.077 and <0.050-0.076 ppm in muscle. Residues increased with increasing feeding levels in liver, but were consistent or declined in the 150- and 500-ppm dose groups for fat and muscle. In tissues, residues of MCPA were highest in kidney, and increased with increasing feeding levels. Residues of MCPA were 0.276-0.410, 0.598-1.20, and 1.66-2.44 ppm in kidney from the 50-, 150-, and 500-ppm dose groups, respectively.

Following cessation of dosing with the test substance, quantifiable residues in whole milk and tissues declined rapidly. Maximum residues of MCPA in milk (0.043 ppm) declined to levels

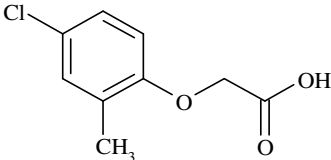
below the LOQ (<0.010 ppm) within 1 day post-dose, and maximum residues in fat (0.133 ppm), liver (0.282 ppm), and muscle (0.076 ppm) declined to levels below the LOQ (<0.050 ppm) within 8 days post-dose. Maximum residues of MCPA in kidney (2.44 ppm) declined to 0.053 ppm by 8 days post-dose.

STUDY DEFICIENCIES

Under the conditions and parameters used in the study, the data are tentatively classified as scientifically acceptable, pending submission of raw data and sample extraction and analysis dates. Raw analytical data to allow verification of reported results (and detector response linearity), and sample extraction and analysis dates to determine sample and extract storage durations for milk and tissues from the subject study are required.

I. MATERIALS AND METHODS

A. MATERIALS

Table B.7.8.1-1. Nomenclature for MCPA.	
Common name	MCPA
Identity	4-chloro-2-methylphenoxyacetic acid
CAS registry number	94-74-6
Company experimental name	None
	

B. STUDY DESIGN

1. Test Procedure

Three groups of dairy cows (3 cows/group) were dosed orally with MCPA in gelatin capsules, once daily after the morning milking for 28 days, at doses equivalent to ~50, 150, and 500 ppm MCPA in the diet (low-, mid-, and high-dose groups, respectively). Three additional cows were administered the high dose for 28 days and then not dosed for 7 days to obtain depuration data. Three control cows received gelatin capsules without MCPA, one control cow for the main study and two for the depuration study. The in-life phase of the study was conducted by Genesis Midwest Laboratories (Neillsville, WI).

Livestock

Table B.7.8.1-2. Description of Livestock Used in the Feeding Study.					
Species	Breed	Age	Weight at Study Initiation (kg)	Health Status	Description of Housing/Holding Area
Dairy cattle	Holstein	3-7 years	463-622	Healthy throughout the study	Individual stalls (4 × 7 feet) with stanchions; wood shavings for bedding material; artificial lighting (14 light/10 dark hours); temperature ranged 14-26 °C and relative humidity averaged 75 ± 4%. Cows were turned out into exercise pens each morning after the morning milking.

Diet

Table B.7.8.1-3. Test Animal Dietary Regime.				
Composition of Diet	Feed Consumption (kg/day) ¹	Water	Acclimation Period	Predosing
3 kg of alfalfa cubes, 3 kg of baled hay, and 4 kg of dairy ration (grain mix) offered twice daily (at each milking); amounts of alfalfa cubes were adjusted based on consumption.	Control Group: 21.3	<i>Ad libitum</i>	7 days	None
	Low-dose Group: 23.1			
	Mid-dose Group: 24.0			
	High-dose Group: 23.3			
	High-dose Group during recovery period: 22.6			

¹ Average feed consumption (dry-weight basis) during dosing period.

Treatment

The test substance was received at the in-life facility and stored at ambient temperatures prior to use. Dosing gelatin capsules were prepared weekly based on the mean daily feed consumption (dry-weight basis) of the dose group for the first four days of the previous week; capsules were stored refrigerated prior to use. Cows were dosed once daily after the morning milking (within 2 hours, except for the last dose) for 28 days.

Table B.7.8.1-4. Dosing Regime.					
Treatment Group (Animal ID #)	Treatment Type	Level of Administered Dose (mg/kg bw/day)	Residue Intake in Diet (ppm)	Vehicle	Duration (days)
Control Group (13, and 11, 18) ¹	Oral using a balling gun	0	0	Gelatin capsule	28
Low-dose Group (10, 15, 16)		1.98	50.3		28
Mid-dose Group (2, 4, 8)		5.89	151.2		28
High-dose Group (3, 5, 6 and 1, 7, 17) ¹		19.58	504.7		28

¹ Control animal #s 11 and 18, and high-dose animal #s 1, 7, and 17 were used for the depuration study.

Sampling

Table B.7.8.1-5. Sample Collection.		
Milk Collected	Interval from Last Dose to Sacrifice	Tissues Harvested and Analyzed
Milk was collected twice daily (AM prior to dosing, and PM). Milk collected in the PM was combined proportionately with milk collected the following AM to generate daily samples. Skim milk and cream were generated from milk samples collected on Study Day 27.	20-24 hours	Liver (distal portion from each lobe), kidney (representative sample from center and both ends of both), muscle (composite of round, flank, and loin), and fat (composite of omental, perirenal, and subcutaneous)

Milk yields were generally consistent for individual animals throughout the study, averaging 21.8, 26.7, 26.6, and 23.0 kg/animal/day for the control, low-, mid-, and high-dose groups, respectively, during the main study, and 20.4 and 23.3 kg/animal/day for the control and high-dose animals, respectively, during the depuration period.

No adverse treatment-related effects were reported on body weight, feed consumption, or milk production, and no treatment-related clinical signs of toxicity were noted. Gross necropsies showed no effects that appeared to be treatment related.

Sample Handling and Preparation

Milk was collected twice daily (evening, and the following morning prior to dosing) during the study period. For each cow, milk from the evening collection was composited proportionately with the next morning sample to produce a daily sample. Evening samples were stored refrigerated overnight until preparation of daily samples, after which they were subsampled into two equal portions and stored frozen (-26 to -12 °C). Additional composited milk collected from the control and 500-ppm dose groups (excluding depuration study cows) on Day 27 was centrifuged to generate skim milk and cream samples, which were also subsampled into two equal portions and stored frozen. One of the equal portions of whole milk, cream, and skim milk was collected for analysis, while the other was retained.

Animals not included in the depuration study were sacrificed within 24 hours after the final dose on Study Day 28. For the depuration study, milk samples were collected on Days 29 and 30, and the 2 control and 3 high-dose cows were terminated on Study Day 36 (8 days post-dose). Samples of liver (distal portion from each lobe), kidney (representative sample from center and both ends of both), muscle (composite of round, flank, and loin), and fat (composite of omental, perirenal, and subcutaneous) were collected from each cow. Individual tissue samples were cubed and frozen (≤ -12 °C), except for fat which was frozen, then cubed, and returned to the freezer. All tissues samples were stored frozen until homogenization in the presence of dry ice; tissues were kept cold during homogenization. Duplicate samples of equal portions were collected (analytical and retention) and all homogenized tissue samples were placed in frozen storage after collection.

Prepared samples were shipped frozen on dry ice by FedEx to the analytical facility, ABC Laboratories, Inc. (Columbia, MO). Samples were stored frozen (ca. -20 °C) at the analytical laboratory.

2. Description of Analytical Procedures

Samples of milk and tissues were analyzed for residues of MCPA using a GC/MSD method adapted from PTRL Report No. 1905, entitled “Development and Validation of Analytical Methodology for the Analysis of 2,4-Dichlorophenoxybutyric Acid (2,4-DB) in Beef Tissues and Milk.” Modification of the method replaced electron capture detection with mass-selective detection.

Briefly, muscle samples were extracted (2x) with acidified acetonitrile (ACN; 1.5% phosphoric acid, v:v). Each extract was centrifuged and/or filtered. The combined extracts were diluted with water, adjusted to pH 2 with concentrated HCl, and partitioned 3x with diethyl ether. The diethyl ether extracts were combined and partitioned 4x with 0.1% NaOH. The combined NaOH extracts were concentrated by rotary evaporation to remove any remaining organic solvent, then acidified to pH 2-3 with concentrated HCl, and cleaned up using C8 and C18 solid phase extraction (SPE) columns placed in series; residues were eluted with methyl-t-butyl ether (MTBE) and concentrated.

Fat samples were blended with hexane, extracted (4x) with 0.1% NaOH, and centrifuged. The aqueous layers were combined and acidified to pH 2-3 with concentrated HCl, then partitioned into diethyl ether and back-extracted into 0.1% NaOH, concentrated, and subjected to SPE cleanup as described above for muscle.

Kidney and liver samples were first refluxed for 2 hours with 4 N HCl, and milk samples were refluxed for 1 hour with concentrated HCl. After cooling, the extracts were diluted with ACN and filtered. NaCl was added to the filtrate to separate the aqueous and ACN layers; the aqueous phase was partitioned two more times with ACN. The combined ACN extracts were then filtered through a Florisil column, and the eluate was diluted with 1% NaOH and concentrated to an aqueous remainder. The aqueous fraction was acidified to pH 2 with concentrated HCl, and partitioned (3x) with 10% ethyl acetate in hexane. The organic layers were added to a neutral alumina column, and residues were eluted with 10% methanol in 1% NaOH. The eluate was acidified to pH 2 with concentrated HCl. MCPA residues were partitioned (3x) into MTBE and the organic phase was concentrated.

MCPA residues in the final milk and tissue fractions were methylated by the addition of boron trifluoride in methanol (BF₃/MeOH) at 70 °C for 30 minutes. After cooling, water and hexane were added and the organic layer was collected for analysis. Residues in milk and tissue fractions were analyzed by GC/MSD by comparison with external MCPA methyl ester standards prepared from MCPA (as MCPA equivalents). The ions monitored were *m/z* 141, 155, 214, and 216. The LOQs (determined as the LLMV) for MCPA were 0.010 ppm for milk, and 0.050 ppm in tissues. The limit of detection (LOD) was not specified, but the study author reported “estimated” residues below the LOQ and identified “not detected” (no peak) as ND.

II. RESULTS AND DISCUSSION

Method performance was evaluated by use of method validation and concurrent recovery samples fortified with MCPA at 0.01-0.1 ppm for milk, 0.01 and 0.05 ppm for cream, 0.05 and 0.5 ppm for fat, liver, and muscle, and 0.05-5.0 ppm for kidney. Recoveries were generally within the acceptable range of 70-120%; therefore, the method was considered valid for the determination of MCPA residues in cow matrices (Table B.7.8.1-6). The fortification levels bracketed the measured residues. Concurrent recoveries were not corrected for apparent residues in controls when applicable.

Representative calibration curves (and raw data) were not provided to demonstrate that the detector response was linear. The study reported that linearity curves were prepared using

MCPA methyl ester standards in MCPA equivalents at 0.15-3.0 µg/mL for milk and tissues. Representative chromatograms of control samples, fortified samples and treated samples were provided. The control chromatograms generally had no peaks of interest above the chromatographic background. The fortified sample chromatograms contained only the analyte of interest, and peaks were symmetrical and well defined. Apparent residues in control samples of milk and tissues were below the LOQ (mostly reported as ND, no peak), except for one milk sample (Day 7) which bore apparent residues of MCPA from triplicate analyses at the LOQ (0.010 ppm), which the study author identified as unexplained contamination. The reported residue values were not corrected for apparent residues in controls.

Table B.7.8.1-6. Summary of Method Validation and Concurrent Recoveries of MCPA from Cow Matrices.					
Matrix	Analyte	Fortification Level (ppm)	Sample Size (n)	Recoveries ¹ (%)	Mean ± Std. Dev. ² (%)
Method Validation					
Milk	MCPA	0.01, 0.1	10	63; 70-107	85 ± 14
Fat	MCPA	0.05, 0.5	10	54 ³ ; 75-100	88 ± 10
Kidney	MCPA	0.05, 0.5	10	81-108	95 ± 10
Liver	MCPA	0.05, 0.5	10	91-118	106 ± 9
Muscle	MCPA	0.05, 0.5	10	75-120; 132 ⁴	104 ± 20
Concurrent Recoveries					
Milk	MCPA	0.01-0.1	33	73-120; 132	97 ± 16
Cream	MCPA	0.01, 0.05	2	109; 127	118
Fat	MCPA	0.05, 0.5	4	74-100	85 ± 12
Kidney	MCPA	0.05-5.0	5	94-107	101 ± 5
Liver	MCPA	0.05, 0.5	4	72-103	86 ± 14
Muscle	MCPA	0.05, 0.5	4	68; 80-87	80 ± 9

¹ Concurrent recoveries were not corrected for apparent residues in controls.

² Standard deviation is not calculated for sample sizes <3.

³ The recovery of 54% was not used in calculation of average and standard deviation; no explanation was provided by the study author.

⁴ The recovery of 132% due to evaporation of the sample extract solvent prior to injection was not used in calculation of average and standard deviation.

The maximum storage intervals for samples between collection and extraction for analysis were not reported; extraction and analysis dates (and raw data) were not provided to independently determine sample storage durations (Table B.7.8.1-7a). However, freezer storage stability data were generated concurrently with the livestock feeding study (Table B.7.8.1-7b). Data showed that MCPA residues were stable in cow milk and tissues under frozen storage for up to 120 days in milk, 112 days in muscle, 134 days in liver, 153 days in kidney, and 173 days in fat. The study author reported that the storage stability study encompassed the storage duration of samples from the feeding study.

Table B.7.8.1-7a. Summary of Storage Conditions.			
Matrix	Storage Temperature (°C)	Actual Storage Duration (days)	Interval of Demonstrated Storage Stability ²
Whole milk	In-life facility: ≤-12; Analytical laboratory: ca. -20	Not reported ¹	MCPA residues are stable for under frozen conditions (ca. -20 °C) for 112 days in muscle, 120 days in milk, 134 days in liver, 153 days in kidney, and 173 days in fat. ²
Cream			
Skim milk			
Tissues			

¹ Dates of extraction and analysis were not provided; therefore, the storage intervals from collection to extraction, and extraction to analysis could not be determined.

² Refer to concurrent storage stability data, Table B.7.8.1-7b.

Table B.7.8.1-7b. Stability of MCPA Residues in Cow Matrices During Frozen Storage.						
Matrix	Spike Level (ppm)	Storage Interval (days)	Fresh Fortification Recoveries (%) [Average]	Stored Sample Recoveries (%)	Mean Recovery (%)	Corrected % Recovery ¹
Milk	0.10	0	96, 94 [95]	--	--	--
		32	109, 117 [113]	118, 91	105	93
		120	105, 87 [96]	94, 99	97	101
Fat	0.50	0	91, 82, 127 [100]	--	--	--
		52	91, 87 [89]	91, 85	88	99
		173	84, 90 [87]	100, 109	105	121
Kidney	0.50	0	99, 118, 119 [112]	--	--	--
		37	93, 98 [96]	85, 86	86	90
		153	111, 108 [110]	115, 100	108	98
Liver	0.50	0	108, 118, 108 [111]	--	--	--
		37	86, 90 [88]	88, 94	91	103
		134	100, 100 [100]	118, 117	118	118
Muscle	0.50	0	90, 108, 98 [99]	--	--	--
		28	101, 114 [108]	95, 97	96	89
		112	103, 104 [104]	113, 119	116	112

¹ Corrected for average recovery in freshly fortified samples.

Residues of MCPA following dosing with MCPA are presented in Table B.7.8.1-8 (whole milk and cream) and Table B.7.8.1-9 (fat, kidney, liver, and muscle). Residues in milk and tissues are summarized in Table B.7.8.1-10.

Residues of MCPA were below the LOQ (<0.010 ppm) in all whole milk samples from the 50- and 150-ppm dose groups. Residues of MCPA in whole milk samples from the 500-ppm dose group were <0.010-0.043 ppm and relatively consistent over time (Figure B.7.8.1-1). Skim milk was not analyzed, but in cream collected on Day 27 from three 500-ppm dosed cows, residues of MCPA were 0.015-0.020 ppm and similar to the corresponding residues in whole milk (0.013-0.022 ppm).

Table B.7.8.1-8. Milk Residue Data from Cattle Feeding Study with MCPA.			
Animal ID #	Collection Time (Dosing Day)	Feeding Level (ppm)	MCPA Residues ¹ (ppm) [Average]
Whole Milk			
10, 15, 16	1	50.3	(0.0007), (0.001), (0.0034) [<0.010]
	7		(0.0038), (0.0025 ²), (0.0050) [<0.010]
	14		(0.0051 ²), (0.0030 ²), (0.0040 ²) [<0.010]
	27		(0.0017), (0.0007), (0.0027) [<0.010]
2, 4, 8	1	151.2	(0.0022), (0.0028), (0.0025) [<0.010]
	7		(0.0047), (0.0057), (0.0045) [<0.010]
	14		(0.0060 ²), (0.0061 ²), (0.0050 ²) [<0.010]
	27		(0.0058), (0.0064), (0.0016) [<0.010]
3, 5, 6 and 1, 7, 17	0	504.7	ND, ND, ND, ND, ND, ND [<0.010]
	1		0.0193, 0.0243, 0.0186, 0.0183, 0.0196, 0.0209 [0.020]
	3		0.0180, 0.0163, 0.0119, 0.0139 ² , (0.0086), 0.0186 [<0.015]
	7		0.0389, 0.0219, 0.0192, 0.0219, 0.0124, 0.0186, 0.0150 [0.021] ³
	11		0.0131, 0.0195, 0.0133, 0.0160, 0.0143, 0.0128 [0.015]
	14		0.0201, 0.0175, 0.0183, 0.0205, 0.0181, 0.0278 [0.020]
	18		0.0167, 0.0174, 0.0148, 0.0127, 0.0160, 0.0189 [0.016]
	21		0.0181, 0.0165, 0.0113, 0.0157, 0.0140, 0.0201 [0.016]
	24		0.0428, 0.0182, 0.0140, 0.0215, 0.0167, 0.0198 [0.022]
	27		0.0216 ⁴ , 0.0207 ⁴ , 0.0134 ⁴ , 0.0229, 0.0263, 0.0309 [0.023]
Cream			
3, 5, 6	27	504.7	0.0145, 0.0196, 0.0171 [0.017]

¹ LOQ for MCPA was 0.010 ppm for milk (and cream). The LOD was not specified, but the study reported “estimated” residues below the LOQ and identified “not detected” (no peak) as ND; raw data were not provided. Estimated residues between the LOD and LOQ are reported parentheses. Dose group averages for each collection day were calculated by the study reviewer using the LOQ for all residues $<LOQ$.

² Average of duplicate analysis.

³ Seven residue values were reported for 6 cows without explanation from the study author; the raw data were not available to confirm the residue values for the 6 cows.

⁴ Whole milk samples corresponding to separated cream samples; average residues of whole milk from the 3 cows was 0.019 ppm.

Following 28 days of dosing with MCPA, residues were below the LOQ (<0.050 ppm) in fat, liver, and muscle samples from the 50-ppm dose group. In samples from the 150- and 500-ppm dose groups, residues of MCPA were, respectively, <0.050 -0.172 and <0.050 -0.133 ppm in fat; <0.050 -0.095 and 0.160-0.282 ppm in liver; and <0.050 -0.077 and <0.050 -0.076 ppm in muscle. Residues increased with increasing feeding levels in liver (maximum MCPA residues in liver by feeding level are graphically presented in Figure B.7.8.1-2), but were consistent or declined in the 150- and 500-ppm dose groups for fat and muscle.

In tissues, residues of MCPA were highest in kidney, and increased with increasing feeding levels. Residues of MCPA were 0.276-0.410, 0.598-1.20, and 1.66-2.44 ppm in kidney from the 50-, 150-, and 500-ppm dose groups, respectively. The maximum MCPA residues in kidney by feeding level are graphically presented in Figure B.7.8.1-3.

Table B.7.8.1-9. Tissue Residue Data from Cattle Feeding Study with MCPA.			
Animal ID #	Collection Time (Dosing Day)	Feeding Level (ppm)	MCPA Residues ¹ (ppm) [Average]
Fat (composite of perirenal, omental, and subcutaneous)			
10, 15, 16	29	50.3	(0.0119), (0.0246), (0.0420) [<0.050]
2, 4, 8	29	151.2	(0.0263), 0.172, 0.119 [<0.114]
3, 5, 6	29	504.7	0.133, 0.116, (0.0350) [<0.100]
Kidney			
10, 15, 16	29	50.3	0.400, 0.276, 0.410 [0.362]
2, 4, 8	29	151.2	0.598, 1.200, 0.627 [0.808]
3, 5, 6	29	504.7	1.660, 2.440, 1.690 [1.93]
Liver			
10, 15, 16	29	50.3	(0.0328), (0.0217), (0.0483) [<0.050]
2, 4, 8	29	151.2	0.0577, 0.0954, (0.0374) [<0.068]
3, 5, 6	29	504.7	0.282, 0.246, 0.160 [0.229]
Muscle (composite of round, flank, and loin)			
10, 15, 16	29	50.3	(0.0162), (0.0145), (0.0195) [<0.050]
2, 4, 8	29	151.2	(0.0239), (0.0461), 0.0772 [<0.059]
3, 5, 6	29	504.7	0.0761, 0.0508, (0.0409) [<0.059]

¹ LOQ for MCPA was 0.050 ppm in tissues. The limit of detection was not specified, but the study reported “estimated” residues below the LOQ and identified “not detected” (no peak) as ND; raw data were not provided. Estimated residues between the LOD and LOQ are reported parentheses. Dose group averages were calculated by the study reviewer using the LOQ for residues reported as <LOQ.

Table B.7.8.1-10. Summary of Residue Data from Cattle Feeding Study with MCPA.								
Matrix	Feeding Level (ppm)	MCPA Residues ¹ (ppm)						Maximum Matrix Residue:Feeding Level Ratio ²
		n	Min.	Max.	Median	Mean	Std. Dev.	
Whole milk (Days 1-27)	50.3	12	<0.010	<0.010	0.010	0.010	N/A	NC
	151.2	12	<0.010	<0.010	0.010	0.010	N/A	NC
	504.7	55	<0.010	0.043	0.018	0.019	0.006	<0.001
Cream (Day 27)	504.7	3	0.015	0.020	0.017	0.017	0.003	<0.001
Fat (composite of omental, perirenal, and, subcutaneous)	50.3	3	<0.050	<0.050	0.050	0.050	N/A	NC
	151.2	3	<0.050	0.172	0.119	0.114	0.061	0.001
	504.7	3	<0.050	0.133	0.116	0.100	0.044	<0.001
Kidney	50.3	3	0.276	0.410	0.400	0.362	0.075	0.008
	151.2	3	0.598	1.20	0.627	0.808	0.340	0.008
	504.7	3	1.66	2.44	1.69	1.93	0.442	0.005
Liver	50.3	3	<0.050	<0.050	0.050	0.050	N/A	NC
	151.2	3	<0.050	0.095	0.058	0.068	0.024	0.001
	504.7	3	0.160	0.282	0.246	0.229	0.063	0.001
Muscle (composite of round, flank, and loin)	50.3	3	<0.050	<0.050	0.050	0.050	N/A	NC
	151.2	3	<0.050	0.077	0.050	0.059	0.016	0.001
	504.7	3	<0.050	0.076	0.051	0.059	0.015	<0.001

¹ The LOQ was 0.010 ppm in milk and cream, and 0.050 ppm in tissues. N/A = Not applicable.

² Referred to as the transfer coefficient (TC) or transfer factor (Tf); to be used in the calculation of residues anticipated at the dietary burden. NC = Not calculated; all residues were at or below the LOQ.

Figure B.7.8.1-1. MCPA Residues in Whole Milk as a Function of Time. Residues are Maximum Values for the 500-ppm Treatment Group.

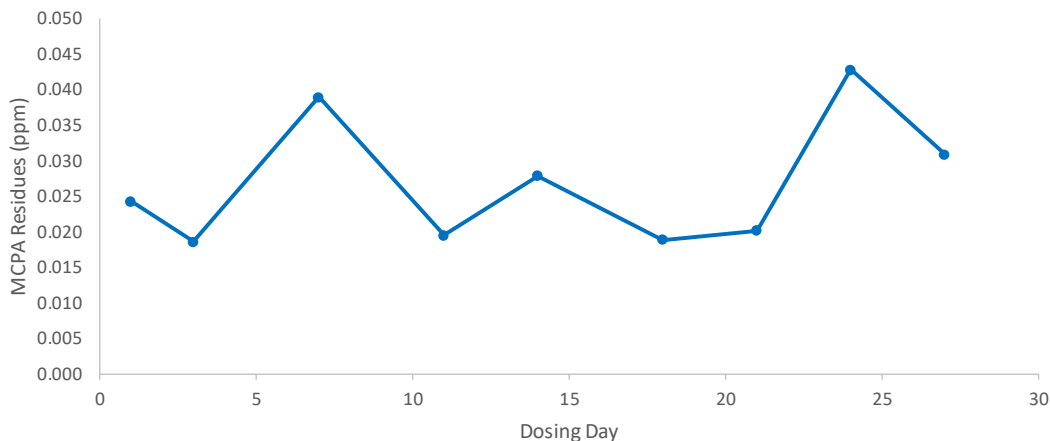


Figure B.7.8.1-2. Linear Regression of Maximum MCPA Residues in Liver on Feeding Level.

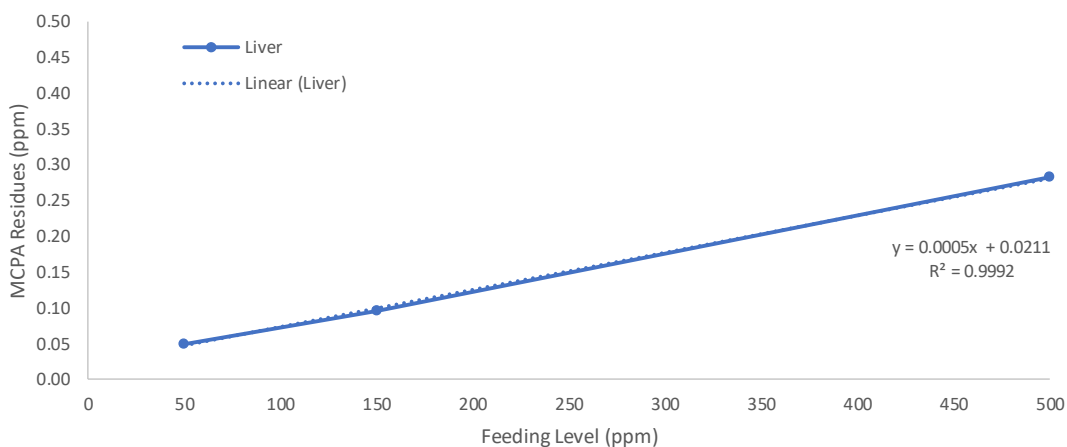
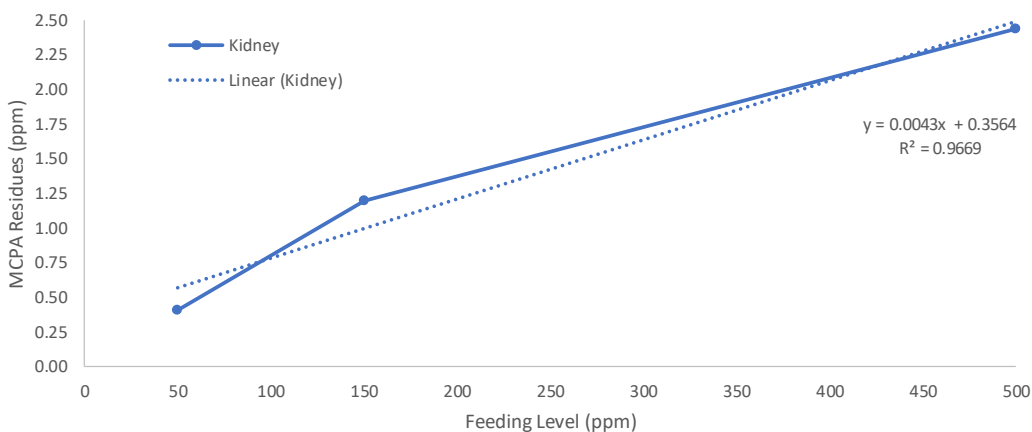


Figure B.7.8.1-3. Linear Regression of Maximum MCPA Residues in Kidney on Feeding Level.



Depuration Period

Following cessation of dosing with the test substance, quantifiable residues in whole milk and tissues declined rapidly. Maximum residues of MCPA in milk (0.043 ppm) declined to levels below the LOQ (<0.010 ppm) within 1 day post-dose, and maximum residues in fat (0.133 ppm), liver (0.282 ppm), and muscle (0.076 ppm) declined to levels below the LOQ (<0.050 ppm) within 8 days post-dose (Table B.7.8.1-11). Maximum residues of MCPA in kidney (2.44 ppm) declined to 0.053 ppm by 8 days post-dose.

Table B.7.8.1-11. Summary of Residues of MCPA in Whole Milk and Tissues of Cows from the Depuration Study.				
Animal ID #	Matrix	Collection Time (Study Day)	Feeding Level (ppm)	MCPA Residues ¹ (ppm) [Average]
1, 7, 17	Milk	29	504.7	(0.0023), ND, (0.0029) [<0.010]
		30		ND, ND, ND [<0.010]
	Fat	36		ND, ND, ND [<0.050]
	Kidney			(0.0383), 0.0526, ND [<0.051]
	Liver			(0.0422), (0.0473), (0.0494) [<0.050]
	Muscle			ND, ND, ND [<0.050]

¹ LOQs for MCPA were 0.010 ppm for milk and 0.050 ppm for tissues. The LOD was not specified, but the study reported “estimated” residues below the LOQ and identified “not detected” (no peak) as ND; raw data were not provided. Estimated residues between the LOD and LOQ are reported parentheses. Dose group averages were calculated by the study reviewer using the LOQ for all residues <LOQ.

III. CONCLUSIONS

The cattle feeding study is tentatively considered scientifically acceptable pending submission of raw data, and sample extraction and analysis dates. The results of the study show that residues of MCPA were below the LOQ (<0.010 ppm) in all whole milk samples from the 50- and 150-ppm dose groups throughout the dosing period. Residues of MCPA in whole milk samples from the 500-ppm dose group were <0.010-0.043 ppm and relatively consistent over time (Days 1-27). Skim milk was not analyzed, but in cream collected on Day 27 from three 500-ppm dosed cows, residues of MCPA were 0.015-0.020 ppm and similar to the corresponding residues in whole milk (0.013-0.022 ppm).

Following 28 days of dosing with MCPA, residues were below the LOQ (<0.050 ppm) in fat, liver, and muscle samples from the 50-ppm dose group. In samples from the 150- and 500-ppm dose groups, residues of MCPA were, respectively, <0.050-0.172 and <0.050-0.133 ppm in fat; <0.050-0.095 and 0.160-0.282 ppm in liver; and <0.050-0.077 and <0.050-0.076 ppm in muscle. Residues increased with increasing feeding levels in liver, but were consistent or declined in the 150- and 500-ppm dose groups for fat and muscle.

In tissues, residues of MCPA were highest in kidney, and increased with increasing feeding levels. Residues of MCPA were 0.276-0.410, 0.598-1.20, and 1.66-2.44 ppm in kidney from the 50-, 150-, and 500-ppm dose groups, respectively.

Following cessation of dosing with the test substance, quantifiable residues in whole milk and tissues declined rapidly. Maximum residues of MCPA in milk (0.043 ppm) declined to levels below the LOQ (<0.010 ppm) within 1 day post-dose, and maximum residues in fat (0.133 ppm), liver (0.282 ppm), and muscle (0.076 ppm) declined to levels below the LOQ (<0.050 ppm) within 8 days post-dose. Maximum residues of MCPA in kidney (2.44 ppm) declined to 0.053 ppm by 8 days post-dose.

An acceptable method was used for residue quantitation, and storage stability data were submitted; however, the raw analytical data and sample extraction and analysis dates are required to determine sample storage durations for milk and tissues from the subject study.

REFERENCES

None.